

# Viewpoints on the Way to the Consensus Session

## Where does insulin resistance start? The adipose tissue

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**A**dipose tissue is a heterogeneous organ with respect to embryonic origin, body distribution, and function. In addition to playing a major role in the regulation of nutrient and energy homeostasis, it is involved in the modulation of the immune response, reproductive function, hemostasis, mechanical support, bone mass growth, and thermogenesis.

To postulate that insulin resistance starts in adipose tissue, there should be evidence of 1) potential mechanisms for such a causal relationship, 2) the manifestation of such mechanisms in insulin-resistant individuals, and 3) their early occurrence in the development of insulin resistance.

**PLAUSIBILITY: ADIPOSE TISSUE CAN CAUSE INSULIN RESISTANCE** — Adipose tissue releases a variety of factors known to modulate insulin sensitivity, and their effects are summarized in Fig. 1.

### Fatty acids

The concept that fatty acids (FAs) provoke cardiac, skeletal muscle, and hepatic insulin resistance and impair  $\beta$ -cell function has been extensively confirmed in humans, and mechanisms are reviewed in detail elsewhere (1). A sustained pharmacologic inhibition of lipolysis, with reduction in the plasma FA concentration, reverses these defects (2–4). Elevated FA levels also promote the synthesis and release of VLDL by the liver by 1) increasing substrate availability, 2) inhibiting insulin-mediated apoB degradation (5), and 3) reducing hepatic insulin clearance, contributing to hyperinsulinemia. In the brain, excessive FA uptake and its re-

sponse to weight loss have been documented in subjects with the metabolic syndrome (6), and FAs are implicated in the central regulation of glucose production (7).

FA overflow from adipocytes to skeletal muscle and other tissues may result in free radical formation during oxidative phosphorylation, the intramyocellular accumulation of triglyceride, and the production of toxic lipid metabolites (fatty-acyl CoAs, diacylglycerol, and ceramides) and metabolic intermediates, which reflect oxidative damage (4), both of which can interfere with the insulin signaling cascade. Consistent with this hypothesis, lipid oxidation is increased systemically and regionally, i.e., in the myocardium and skeletal muscle, and in the liver in states of insulin resistance and/or in steatosis (8–10), and recent evidence supports a role of  $\beta$ -cell oxidative stress in mediating FA-induced  $\beta$ -cell dysfunction (11). Local production of reactive oxygen species within adipose tissue likely initiates lipotoxicity and insulin resistance at the immediate site of FA release (12). Oxidative damage is amplified by peroxidation of lipid stores and could, in turn, impair mitochondrial function and insulin sensitivity and produce inflammation in different target organs.

### Adipokines

Adipose tissue is the largest endocrine organ in the body and generates multiple signals that regulate metabolism in other tissues. Leptin acts centrally to enhance the resting metabolic rate and decrease appetite, thus reducing tissue triglyceride accumulation. In lipodystrophic humans with severe insulin resistance, the admin-

istration of leptin restores insulin sensitivity and reduces organ steatosis and hyperglycemia (13). However, leptin deficiency and resistance are rare causes of disease in humans. Interestingly, leptin receptors have been identified in the vessel wall, and leptin infusion increases arterial blood pressure (14). Adiponectin is produced by adipose tissue in inverse amounts to the fat mass and is one relevant mediator of the action of peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) agonists. Administration of adiponectin reverses the insulin resistance associated with obesity or lipodystrophy by reducing FA and triglyceride levels (15). Plasma adiponectin concentrations typically are reduced in obese normal glucose tolerant, insulin-resistant and lean, and obese type 2 diabetic subjects, and decreased plasma adiponectin levels are predictive of hepatic steatosis and insulin resistance. However, the observation that weight loss has a dramatic effect on insulin sensitivity without change in the plasma adiponectin concentration mitigates against a causal role of this hormone in the pathogenesis of insulin resistance (16). The role of resistin, which is elevated in animal models of obesity and diabetes, and of visfatin and omentin (which are produced by visceral fat) in the development of insulin resistance remains controversial.

### Adipocytokines

Tumor necrosis factor (TNF)- $\alpha$  stimulates adipose tissue lipolysis, promotes VLDL production (17), interferes with insulin signaling and expression of adiponectin, and increases the expression of interleukins. In humans, tissue expression, rather than circulating levels of TNF- $\alpha$ , correlates with obesity and insulin resistance (18). Interleukin (IL)-6 also is associated with insulin resistance, increased fat mass, and elevated circulating FA levels, consistent with the lipolytic action of this cytokine. IL-6 interferes with the insulin signaling pathway in hepatocytes, skeletal muscle, and adipose tissue (19) and inhibits the production of adiponectin.

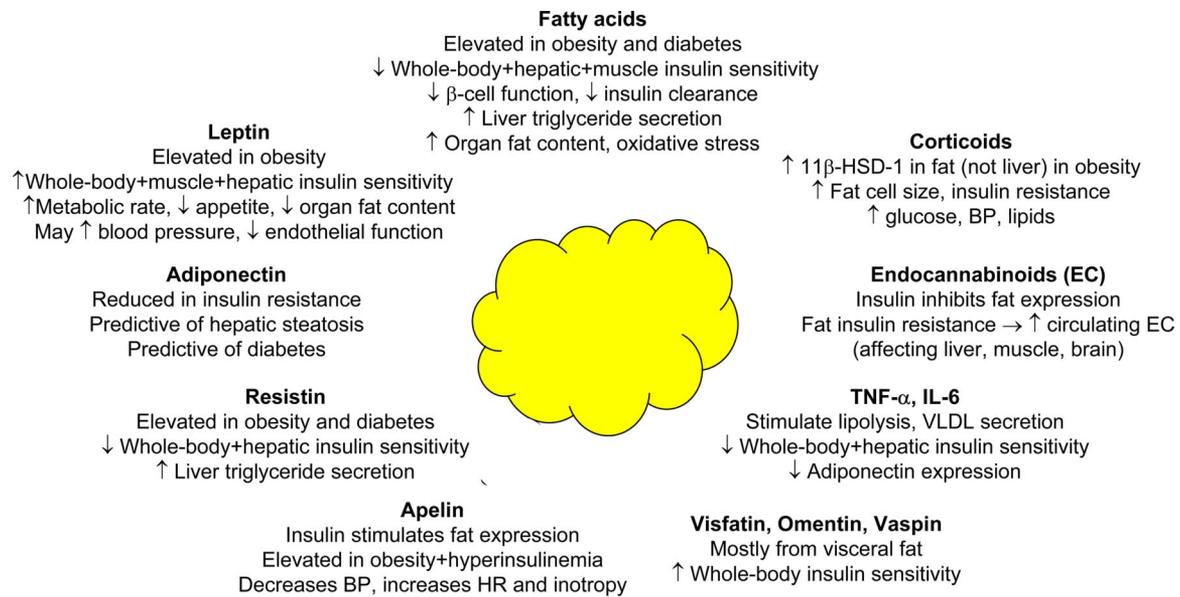
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**Figure 1**—Adipose tissue is the largest endocrine organ in the body. The diagram summarizes the main roles and effects of representative fat-derived products that have been related to insulin resistance and metabolic risk. BP, blood pressure; HR, heart rate.

### Glucocorticoids and endocannabinoids

Sex steroids and corticosteroids have a major impact on fat distribution and enzymes involved in steroid synthesis and metabolism, such as 11-β hydroxysteroid dehydrogenase (11-β-HSD1) (20) and aromatase, and are present in adipose tissue. Activation of 11-β-HSD1 results in tissue-specific glucocorticoid excess, causing central obesity with increased fat cell size, insulin resistance, hyperglycemia, hyperlipidemia, and hypertension. In obese Zucker rats, adipose, but not hepatic, tissue expression of 11-β-HSD1 is increased. In humans, subcutaneous adipose tissue expression and activity of 11-β-HSD1 correlate with indexes of obesity.

In adipose tissue, fat-specific overproduction of endocannabinoids reduces adiponectin expression, decreases adipose tissue energy expenditure and fat oxidation, and enhances lipogenesis. Recent evidence demonstrates that insulin inhibits the synthesis of endocannabinoids and that fat-specific insulin resistance may be responsible for the augmented plasma endocannabinoid levels found in insulin-resistant states. The increased plasma endocannabinoid levels could influence liver, muscle, and brain regulation of glucose homeostasis (21).

**EVIDENCE FOR ADIPOSE TISSUE DYSFUNCTION AND ALTERED TOPOGRAPHY IN INSULIN RESISTANCE**— By buffering postprandial FA influx, adipose tis-

sue plasticity plays an important role in controlling nutrient supply to other organs, and the ability of adipocytes to dispose of ingested fat load is impaired in both obesity and lipodystrophy (22). Adipose tissue is composed of adipocytes, pre-adipocytes, nerves, macrophages, fibroblasts, and vascular cells, and this constitutes a network that can lead to a variety of dysfunctional manifestations.

### Adipocyte size and buffering ability

Adipocytes can maximally store ~0.8 μg lipid per cell. Larger adipocytes become insulin resistant, leading to reduced triglyceride and glucose clearance. Lean offspring of type 2 diabetic subjects, who do not manifest overt insulin resistance and who have no apparent metabolic or hemodynamic abnormalities (23), have a significant enlargement in adipocyte size, enhanced regional subcutaneous glycerol release in response to insulin, and normal FA levels. In Pima Indians, large fat cell volume and circulating FA levels are an independent predictor of the future development of diabetes (24). Interventions that reduce adipocyte size, either by increasing the total amount of fat via recruitment of new adipocytes (e.g., thiazolidinediones) or by depleting triglyceride stores in existing fat cells (e.g., exercise, diet), reverse most of the features associated with fat dysfunction. Smaller adipocytes have more buffering capacity, and this may explain the link between the decrease in adipocyte size and reversal of insulin resistance. Indeed,

*ob/ob* PPAR-γ2 knockout mice are lean and have a reduced number of small adipocytes. They develop an early defect in GLUT4 expression in adipose tissue, severe insulin resistance, β-cell failure, and dyslipidemia (25).

### Adipose tissue metabolism, perfusion, and inflammation

Adipose tissue accounts for 10–20% of whole-body glucose utilization. Insulin-mediated glucose disposal is impaired in obese nondiabetic subjects and patients with type 2 diabetes. It has been suggested that expansion of fat mass partly compensates for the defect in insulin action, supporting a role for adipose tissue in attenuating insulin resistance (26). Notably, fat-specific GLUT4 deletion causes whole-body insulin resistance, whereas muscle GLUT4 ablation stimulates adipose tissue glucose disposal (27). Recent data in humans document higher fasting FA uptake in adipose tissue in obese subjects (28). Circulating FA levels are typically increased in insulin-resistant states and generally correlate with the severity of insulin resistance; normal FA levels may be observed, if a compensatory increase in FA clearance occurs. An acute increase in FFA concentrations in normal subjects leads to acute cellular inflammation, as revealed by the increase in nuclear factor κB and macrophage migration inhibitory factor. Both of these factors have been implicated as potential causes of insulin resistance, thus suggesting an addi-

tional indirect mechanism of FA-induced insulin resistance (29).

Adipose tissue blood flow is reduced in obese nondiabetic and type 2 diabetic subjects (22), and this could lead to a defect in triglyceride clearance by adipocytes and FA spillover from adipose tissue. The perfusion defect may be due, in part, to adipocyte enlargement, which cannot be compensated by adequate angiogenesis (30). The diameter (140–180  $\mu\text{m}$ ) achieved by enlarged adipocytes is greater than the diffusion distance of oxygen, thus limiting the exchange between blood and adipocyte cytoplasm. Hypoxia may inhibit adipocyte differentiation and adiponectin expression, promote formation of free radicals and inflammation (31), and lead to cell death. Consistent with this, macrophages in adipose tissue are localized primarily around dead adipocytes (32). Increased numbers of macrophages in fat are observed in obese individuals, and newly recruited macrophages have a greater increase in proinflammatory properties than resident ones (33). Inflammation and macrophage infiltration intensify with increasing obesity and can be reversed by weight loss (34).

### **Adiposity and fat topography**

In humans, white adipose tissue is found in the subcutaneous, intra-abdominal, epicardial, extramyocellular, perivascular, lymphnodal, retroorbital, and facial regions. It also is present in bone marrow and mammary gland. Brown fat occurs during fetal development, with some remnants in the mediastinal, paravertebral, and neck areas in adults (35). Each depot has specific gene expression and different responsiveness to nutrients, hormones, and temperature, thereby reflecting specific tasks. Metabolically active fat in the intra-abdominal, intermuscular, perivascular, and epicardial areas may serve for the immediate provision of energy to respective vital organs (i.e., liver, heart, vessels, and skeletal muscle). By directly providing FAs to the liver, visceral fat also represents a source of ketones for the brain. Omental fat acts as a sensor that regulates the disposal of ingested nutrients and directs their delivery from the liver to the rest of the body, with feedback to the brainstem through autonomic neurons (36). Deep subcutaneous adipose tissue in the trunk is restrained by the fascia superficialis and can nourish the underlying extensive muscle apparatus. These adipose depots share similarities in adipocytokine and FA release patterns

and display resistance to insulin (37–39). Compared with visceral adipocytes, superficial subcutaneous adipose tissue primarily serves as a storage organ, consistent with its anatomical location, response to the anabolic action of insulin, and its more efficient proliferation and differentiation *in vitro* (40). Thus, relative insulin resistance in intra-abdominal fat and intrathoracic and intermuscular depots optimizes their ability to release energy to proximal organs, while limiting the expansion upon surrounding structures.

Epidemiological evidence demonstrates that obesity, high energy intake, and sedentary lifestyle are significant contributors to the epidemic of chronic disease, i.e., type 2 diabetes and atherosclerosis, related to insulin resistance. However, despite similar lifestyles, 1) some subjects are more susceptible to weight gain than others; 2) insulin sensitivity varies over a wide range in obese and lean individuals; 3) ~20% of obese individuals do not develop metabolic abnormalities, whereas 18% of lean subjects do (41); and 4) elderly individuals, offspring of diabetic parents, and lipodystrophic subjects are typically insulin resistant despite a lean phenotype.

These apparent incongruities can be reconciled by postulating that a defect in subcutaneous adipose tissue expandability, independent of body weight or adiposity, may be the primary cause of insulin resistance. In fact, hyperplastic obesity—in which newly differentiated adipocytes maintain the ability to store triglycerides—is typically more benign than fat hypertrophy. Longitudinal studies in Pima Indians (42) have documented that insulin-sensitive subjects, in whom the anabolic effect of insulin is enhanced, gain more weight and have a fourfold more rapid decline in insulin sensitivity than less insulin-sensitive individuals. Thus, both fat mass and insulin resistance should be regarded as relative and dynamic features, and this could explain the relatively weak correlation between the two variables.

The primacy of defective subcutaneous fat storage versus visceral fat enlargement in the development of metabolic complications is supported by evidence in patients with total lipodystrophy, who experience severe insulin resistance despite the lack of visceral fat. In addition, treatments that selectively augment the ability of subcutaneous tissue to take up and store fat (including glitazones in humans and subcutaneous fat re-implantation in

animals [43]) have a major impact to reverse insulin resistance and normalize metabolic risk factors without modifying (or even increasing) the total mass of ectopic fat depots. Conversely, liposuction fails to correct the metabolic disturbances, i.e., insulin resistance and glucose intolerance, in obese humans (44); this may be partly accounted for by the fact that lifestyle is not modified, and macronutrient intake is a demonstrated source of oxidative stress and inflammation, potentially interfering with insulin signaling (45–47). Subcutaneous tissue is at least 10-fold larger than visceral fat mass, and its production of FAs and adipokines outweighs the contribution of those from nonsubcutaneous fat depots. The immediate consequence of a defect in subcutaneous storage capability is the uncontrolled outflow of substrates (FAs) and compensatory expansion of alternative fat depots or deposition of triglycerides in nonadipose tissues. Thus, removal of part, or all, of a fat depot leads to expansion of alternative fat tissue (48).

A high visceral-to-subcutaneous fat mass ratio correlates closely with the metabolic syndrome phenotype in obese and lean individuals (41) and is a typical feature of aging and lean insulin-resistant offspring of type 2 diabetic individuals. Targeted expansion of the visceral fat mass by steroids and the selective surgical removal of visceral fat in animals (49) and omental fat in humans (50) support the detrimental role of this depot. Numerous large cohort studies have demonstrated that excessive visceral, intermuscular, and trunkal fat mass correlates with the severity of metabolic dysregulation, cardiovascular risk, and presence of type 2 diabetes (51–53). Smaller adipocyte size was shown to be associated with increased leg fat mass, whereas larger adipocyte size was related to more trunkal fat mass (53).

In summary, the inability of adipose tissue to store FA and glucose, independent of total body adiposity, appears to be a common feature in all disorders characterized by insulin resistance. The fat insulin resistance is related to excessive FA accumulation and cell enlargement. Oxidative stress in fat cells is exacerbated by reduced perfusion and relative hypoxia, which promote chemo-attraction and inflammation. These abnormalities adversely influence metabolic pathways throughout the body in the form of lipotoxicity, ectopic fat storage, systemic low-grade inflammation, and insulin resistance. Epi-



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